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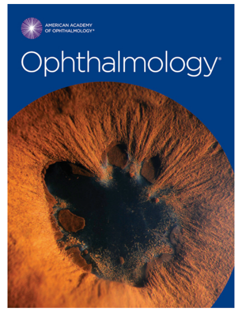

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Autologous Retinal Transplantation for Primary and Refractory Macular Holes, and Macular Hole Retinal Detachments: The Global Consortium

Short Title: ART for Macular Holes

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Abstract

PURPOSE: To report the anatomical and functional outcomes of autologous retinal transplantation (ART).

DESIGN: Multicenter, retrospective, interventional, consecutive case series.

PARTICIPANTS: 130 eyes of 130 patients undergoing ART for the repair of primary and refractory macular holes, as well as combined macular hole-rhegmatogenous retinal detachments (MH-RRD), between January 2017 and December 2019.

METHODS: All patients underwent pars plana vitrectomy and ART, with surgeon modification of intraoperative variables. A large array of preoperative, intraoperative, and post-operative data was collected. Two masked reviewers graded optical coherence tomography (OCT) images. Multivariate statistical analysis and subgroup analysis were performed.

MAIN OUTCOME MEASURES: Macular hole closure rate, best corrected visual acuity (VA), external limiting membrane, ellipsoid zone (EZ) integrity, and alignment of neurosensory layers (ANL) on OCT.

RESULTS: 130 ART surgeries were performed by 33 vitreoretinal surgeons worldwide. Patient demographics were: mean age 63±6.3 years, 58% females, 41% Caucasian, 23% African, 19% Asian, and 17% Latino. Preoperative logMAR VA was 1.37±0.12 (~20/500), which improved significantly to 1.05±0.09 (about 20/225; $p<0.001$) postoperatively (mean follow-up 8.6±0.8 months). ART was performed for primary macular hole repair in 27% of cases (n=35), for refractory macular holes in 58% of cases (n=76; mean number of previous surgeries 1.6±0.2), and MH-RRD in 15% of cases (n=19). Mean maximum macular hole diameter was 1470±160 µm, mean minimum diameter was 840±94 µm, and mean axial length was 24.6±3.2 mm. Overall, 89% of macular holes closed (78.5% complete, 10% small eccentric defect), with a 95% closure rate in MH-RRD (68.4% complete, 26.3% small eccentric defect). VA improved by at least 3 lines in 43% of eyes and at least 5 lines in 29%. Reconstitution of the EZ ($p=0.02$) and ANL ($p=0.01$) on OCT were associated with better final VA. There were 5 cases of ART graft dislocation (3.8%), 5 cases of postoperative retinal detachment (3.8%), and 1 case of endophthalmitis (0.77%).

CONCLUSION: In this global experience, patients undergoing ART for large, primary and refractory macular holes, and MH-RRDs, achieved good anatomical and functional outcomes, with low complication rates despite complex surgical pathology.

Introduction

The development of autologous retinal transplantation (ART) in 2016 as a surgical technique has unlocked new avenues for addressing challenging macular holes (MHs).[1] Since the seminal paper, the technique has been performed by numerous surgeons around the world, with many modifications including combined neurosensory retina – retinal pigment epithelium – choroid grafts,[2] subretinal placement of the graft,[3] and for the primary treatment of large, chronic macular holes.[4] Indeed, the idea of using a graft to close a macular hole, has expanded the surgical approach and enhanced the armamentarium of many surgeons; additional methods of grafting have since been performed, including using human amniotic membranes as an implantable graft.[5]

Whether for myopic macular holes, refractory MHs, large to giant primary MHs, or combined macular hole – rhegmatogenous retinal detachments (MH-RRD), the ability to close the hole with ART, has made surgery possible for cases that could not be previously addressed. Since the initial report of vitrectomy for macular hole repair in the early 1990s,[6] the surgical approach for macular hole repair has involved addressing tractional vectors: (1) antero-posterior traction and (2) tangential traction; whether by vitrectomy alone, vitrectomy with membrane and/or internal limiting membrane (ILM) peeling, or with an ILM flap.[7-11] Other techniques, such as radial perifoveal incisions, ILM free flaps, and subretinal expansion with balanced salt solution have also been described.[12-15] Grafting procedures, such as ART and amniotic membrane grafts, have allowed surgeons to treat macular holes by way of a third mechanism: by using a scaffold to promote centripetal migration of macular hole edges in the case of an amniotic membrane or the addition of tissue through ART. Some surgeons have also used blood products as an adjuvant to encourage adherence of the transplant to the foveal graft site.[16-18]

A multicenter pilot study was recently published, to determine whether ART is feasible in the hands of different surgeons.[19] In that study, four surgeons demonstrated an 87.8% macular hole closure rate in 41 patients with refractory macular holes that had failed previous vitrectomy with ILM peeling and gas tamponade. Based on the results of that study, we were motivated to determine what the real-world, global outcomes would be for cases of ART, and the ART Global Consortium was created.

Methods

An open invitation for the contribution of surgical cases of Autologous Retinal Transplantation (ART), from any surgeon wishing to participate, was announced at multiple meetings and throughout different societies and by emails worldwide. Surgeons were invited to contribute consecutive cases of ART for patients undergoing repair of a primary macular hole, a refractory (persistent or recurrent) macular hole, or a combined MH-RRD. Surgeons were encouraged to contribute all cases, regardless of the outcome, including a description of their intraoperative surgical technique, preoperative and postoperative deidentified data, and ancillary testing.

A standardized data collection sheet was distributed to all surgeons. Surgical cases performed between January 1, 2017 and December 31, 2019 were accepted for inclusion. This study complied with the Health Insurance Portability and Accountability Act of 1996 and adhered to the tenets of the Declaration of Helsinki. An independent Institutional Review Board approved this study and deidentified patient data was collected.

All patients underwent pars plana vitrectomy and autologous retinal transplantation, with modification of intraoperative variables as desired by the surgeon. A large array of data was collected regarding the surgical techniques, anatomic outcomes, and functional outcomes.

Preoperative and intraoperative variables, including minimum and maximum macular hole diameter, axial length, lens status, retinal graft size, harvest site, tamponade agent, and intraoperative and postoperative complications, were assessed. Color fundus photography, autofluorescence, and optical coherence tomography (OCT) were performed at various time points using a commercially available spectral-domain OCT device (Spectralis HRA OCT, Heidelberg, Germany or Topcon SD-OCT, Tokyo, Japan) or swept source OCT device (DRI OCT Triton, Topcon, Tokyo, Japan). Widefield fundus photography (Optos, Marlborough, MA), OCT angiography (Carl Zeiss Meditec, Inc., Dublin, CA, or Optovue, Inc., Fremont, CA), microperimetry (MAIA, CenterVue, Padova, Italy), and multifocal electroretinography were performed when possible.

The primary outcome measured was anatomic macular hole (MH) closure. Secondary outcomes analyzed were numerous, and they included but were not limited to: best corrected visual acuity at various time points, subjective patient experience, complication rates, and analysis of ancillary testing. Two masked reviewers independently evaluated the OCT images and graded them using a standardized approach. The following features were assessed: (1) anatomic closure by OCT (complete vs eccentric; whereby for these unusually large to giant holes, eccentric closure was defined on OCT by subfoveal closure of the hole with a small sliver of eccentric peripheral opening less than 10% of the area of the original hole, at least ~500 μm from the foveal center), (2) reconstitution of the external limiting membrane (ELM) and ellipsoid zone band and the timing thereof, (3) alignment of neurosensory layers (ANL; a novel finding presented herein, whereby the donor graft and surrounding host retina integrate in such a way as to line up layer by layer), (4) transient hyperreflectivity of the ART graft suggestive of transient hypoxia, and (5) hyperreflective foci suggestive of the presence of microglia. Additional ancillary testing, such as fluorescein angiography, OCT angiography, autofluorescence, microperimetry, and multifocal electroretinography, was reviewed, when available.

Multivariate statistical analysis was performed. Subgroup analysis was performed for primary macular holes, refractory (recurrent + persistent) macular holes, and combined MH-RRDs. Statistical analysis was performed using SPSS (SPSS 26, Chicago, IL, USA). Recorded visual acuity (VA) measurements, including Early Treatment of Diabetic Retinopathy Study (ETDRS) and Snellen VA were converted to logarithm of the minimum angle of resolution (logMAR) VA. Counting fingers and hand movement were defined as 0.01 (20/2000 snellen, 2.0 logMAR) and 0.001 (20/20000 snellen 3.0 logMAR), respectively. Visual improvement was defined as an increase of at least 0.3 logMAR units, and decline was defined as a decrease of at least 0.3 logMAR units (equivalent to 15 ETDRS letters). Descriptive statistics were computed. Nonparametric t-tests were utilized since the data was not normally distributed. P-values < 0.05 were considered statistically significant. Multivariate analysis of variance (ANOVA) was performed. The variables were first assessed for normality by Levine's test of equality and were found to be approximately normally distributed. A post hoc Tukey test was selected for further analysis.

Results

Case Selection and Patient Demographics

Thirty-three surgeons from around the world contributed their cases. There were 130 consecutive surgeries performed on 130 eyes of 130 unique patients (Table 1). All cases reported by surgeons were analyzed and those included primary macular holes (n=35; 27%), refractory macular holes (n=76; 58%), and combined MH-RRDs (n=19; 15%; of which 68.4% (13/19) had undergone previous vitrectomy and 63.2% (12/19) had undergone previous ILM peeling). The mean patient age was 63±6.3 years and 58% of patients were female. The racial and ethnic backgrounds of the patients were diverse: 41% Caucasian, 23% African, 19% Asian, and 17% Latino.

Surgical Technique

Three-port 23- or 25-gauge pars plana vitrectomy (Constellation, Alcon, Fort Worth, TX, USA; or EVA, DORC International, Zuidland, Netherlands; or Stellaris Elite, Bausch & Lomb, Inc., Rochester, NY, USA) was performed with retrobulbar or peribulbar anesthesia using monitored anesthesia care or under general anesthesia. Most cases were done uni-manually with either the pneumatic scissors (Alcon or DORC) or the vitrector in one hand and the light pipe in the other. A 25-gauge chandelier illuminator (Alcon) was used to facilitate bimanual maneuvers when necessary. Brilliant Blue (Doubledyne, Alfaintes, Italy) or indocyanine green dye solution (25 mg ICG in 20 mL 5% dextrose-water solution) or ILM Blue (DORC) was delivered to the retinal surface around the macular hole to confirm the status of the ILM. The surgical techniques and instrumentation were left to the discretion of the individual surgeon.

As previously described, a neurosensory or combined retina and choroid graft was selected, with some surgeons choosing a donor site between the arcades and the equator (posterior) and others choosing a site peripheral to the equator (anterior). Surgeons chose to harvest from various sectors: superonasal, superior, superotemporal, temporal, inferotemporal, inferior, inferonasal, and nasal. The size of the graft was at the discretion of the surgeon and was recorded as a multiple of the optic disc (e.g. 1 disc diameter, 2 disc diameters, etc). Barrier endolaser treatment was delivered in multiple rows around the graft harvest site, as well as endodiathermy to cauterize blood vessels at the edges of the graft site in most cases. The graft itself was harvested from healthy retinal tissue within the barrier zone of endolaser so that the edges of the graft were not affected by laser or diathermy.

Most surgeons performed the transfer of the ART graft to the macular hole under perfluoro-n-octane (PFO; Perfluoron; Alcon, Fort Worth, TX) for stability. The edge of the graft was held, if required, using end-grasping forceps (e.g. Alcon 23-g or 25-g Max Grip or ILM forceps, Fort Worth, TX). The graft was cut using vertical or curved scissors (Alcon 23-g or 25-g Revolution DSP Vertical or Curved Scissors or 23-g Pneumatic Scissors, Fort Worth, TX) or the vitrector. The graft was then transferred to its intended site, at the macular hole, with some surgeons leaving it preretinally or at the level of the retina, and others tucking it subretinally. Some surgeons chose to leave PFO as a short-term tamponade, while others performed a fluid-air exchange and then delivered either silicone oil (SO) or diluted gas (sulfur hexafluoride SF6 or perfluoropropane C3F8) as the tamponade agent; other surgeons performed a direct PFO to SO exchange. All sclerotomies were either closed with a single interrupted suture or noted to be self-sealing after external tamponade. The patients were positioned face down post-operatively for 3 to 7 days depending on surgeon preference (in the case of gas or SO), except when PFO was used as tamponade, in which case patients were positioned supine. The timing of SO or PFO removal were at the discretion of the surgeon.

Intraoperative Surgical Variables

Ninety percent of transplants were taken from neurosensory retina alone, while 10% were harvested deeper to include neurosensory retina, retinal pigment epithelium, and choroid. Grafts were harvested from the following locations: 45% superiorly, 17% inferonasally, 11% superotemporally, 8% inferiorly, 8% superonasally, 7% temporally, and 4% inferotemporally. The graft was harvested posterior to the equator in 84% of cases and anterior to the equator in 16% of cases. The graft was positioned preretinally or in the same plane as the host retina in 81% of cases, and it was tucked subretinally in 19% of cases. Some surgeons aimed to oversize the ART donor graft relative to the macular hole (40%), while others aimed to fit it edge-to-edge with the host tissue (60%); intraoperatively, grafts measured up to 1 disc diameter in 70% of cases, 1 to 2 disc diameters in 29%, and 2 to 3 disc diameters in 1%.

Seventy-two percent of cases were performed with 23-gauge vitrectomy and 28% with 25-gauge vitrectomy. PFO was used during almost every case in order to assist with harvesting and delivering the transplant. The final tamponade agent used at the end of the case was silicone oil in 60% of cases, PFO in 20% of cases, and gas in 20% of cases. In cases where intraoperative exchange of tamponade agent was performed: a PFO to air exchange followed by delivery of silicone oil or gas was performed in 72% of cases; a direct PFO to silicone oil exchange was performed in the other 28% of cases.

Intraoperative complications were rare. There were 3 cases of intraoperative graft slippage (2.3%), 2 cases of undersized graft (1.5%), 1 case of subfoveal retinal pigment epithelium (RPE) damage (0.8%), and 4 cases of intraoperative bleeding (3.1%).

Anatomic Outcomes for Primary and Refractory Macular Holes

There were 35 cases of ART performed for primary macular holes (27% of cases; Table 2A). Most patients were phakic (77%). Mean maximum macular hole diameter was 1480±297 µm, and the mean minimum macular hole diameter was 882±176 µm. The mean axial length was 23.1±4.9 mm, and the mean spherical equivalent was -0.95 ±0.20. There was an 85.7% macular hole closure rate after ART surgery; 97% of anatomic closures were complete, compared to 3% eccentric. There was 1 case of graft dislocation (2.9%) and 1 case of post-operative proliferative vitreoretinopathy (2.9%; PVR). Of phakic patients, 11% underwent cataract extraction with intraocular lens placement (CEIOL) during the study period.

There were 76 cases of ART performed for refractory macular holes (58% of cases; Table 2B). Most patients were pseudophakic (57%). Mean maximum macular hole diameter was 1440±210 µm, and the mean minimum macular hole diameter was 796±117 µm. The mean axial length was 24.8±4.6 mm, and the mean spherical equivalent was -2.4 ±0.40. There was an 88% macular hole closure rate after ART surgery; 89% of anatomic closures were complete, compared to 11% eccentric. There were 3 cases of graft dislocation (4.0%), 1 case of post-operative retinal detachment (1.3%), 1 case of endophthalmitis (1.3%), 2 cases of subfoveal RPE damage (2.7%), and 5 cases of subretinal or vitreous hemorrhage (6.6%). Of phakic patients, 12% underwent CEIOL during the study period.

Visual Acuity Outcomes for Primary and Refractory Macular Holes

In the primary macular hole group, preoperative mean logMAR visual acuity was 1.090±0.184 (Snellen equivalent of 20/246), which improved significantly to 0.838±0.142 (Snellen equivalent of 20/138; p=0.003) postoperatively (mean follow-up 8.5±1.4 months; Table 2A). There were 37% of patients who experienced a 3-line gain in visual acuity and 17% who gained at least 5-lines.

In the refractory macular hole group, preoperative mean logMAR visual acuity was 1.258±0.144 (about 20/362), which improved significantly to 1.063±0.123 (about 20/231; p=0.002) postoperatively (mean follow-up 8.6±1.0 months; Table 2B). There were 37% of patients who experienced a 3-line gain in vision and 25% who gained at least 5-lines.

OCT Analysis of Post-operative Anatomical Outcomes for Primary Macular Holes

In the primary macular hole group, 24 cases with macular hole closure had OCTs of sufficient quality and follow up for anatomical analysis. Two masked reviewers independently reviewed the images and graded them using a standardized approach. Thirteen cases demonstrated reconstitution of the external limiting membrane (ELM; 54%) at a mean of 2±0.72 months (Figure 1). Twelve cases conveyed reconstitution of the ellipsoid zone band (EZ band; 50%), at a mean of 5.8±1.5 months. Four cases demonstrated alignment of neurosensory layers (ANL; 17%; Figure 2), a novel OCT finding, in which the layers between the donor graft and host retina appear to align (e.g. inner plexiform to inner plexiform, outer plexiform to outer plexiform, etc).

OCT Analysis of Post-operative Anatomical Outcomes for Refractory Macular Holes

In the refractory macular hole group, 39 cases of macular hole closure had OCTs of sufficient quality and follow up for anatomical analysis (Table 2B). Twenty-six cases demonstrated reconstitution of the ELM (67%) at a mean of 2.5±0.60 months. Twenty-six cases conveyed reconstitution of the EZ band (67%), at a mean of 3.2±0.46 months. Eight cases demonstrated ANL (21%).

Outcomes for Combined MH-RRDs

There were 19 cases of ART performed for combined macular hole – rhegmatogenous retinal detachments (15% of cases; Table 2C). Most patients were pseudophakic (68%). Mean maximum macular hole diameter was 1630±576 μm, and the mean minimum macular hole diameter was 932±330 μm. The mean axial length was 28.0±9.3 mm, and the mean spherical equivalent was -10.3 ±2.9. There was a 95% macular hole closure rate after ART surgery; 72% of anatomic closures were complete, compared to 28%, which were partial or eccentric closures. There was a 79% retinal reattachment rate with a single surgery; in 66.7% of these cases, the final tamponade agent (silicone oil, PFO, gas) had been removed or resolved by the date of study closure. There was 1 case of graft dislocation (5.3%), 4 cases of post-operative retinal detachment (21%) due to proliferative vitreoretinopathy, and 2 cases of subretinal PFO (11%). The preoperative mean logMAR visual acuity was 2.316±0.531 (about Hand Motion vision), which improved significantly to 1.403±0.322 (Snellen equivalent of 20/500; p<0.001) postoperatively (mean follow-up 8.9±2.0 months). There were 74% of patients who experienced a 3-line gain in vision and 68% who gained at least 5 lines. Of phakic patients, 17% underwent CEIOL during the study period.

OCT Analysis of Post-operative Anatomical Outcomes for Combined Macular Hole – Rhegmatogenous Retinal Detachments

In the combined macular hole – rhegmatogenous retinal detachment group, 17 cases of macular hole closure had OCTs of sufficient quality and follow up for anatomical analysis (Table 2C). Five cases demonstrated reconstitution of the ELM (29%) at a mean of 1.9±0.60 months. Four cases conveyed reconstitution of the EZ band (24%), at a mean of 1.5±0.29 months, and the reconstitution was partial in 3 of those 4 cases. One case demonstrated ANL (5.9%).

Multivariate Analysis of Factors Affecting Macular Hole Closure Rates

Multivariate analysis showed no statistically significant association between any preoperative patient characteristics and the rate of macular hole closure (Table 3). Likewise, there was no statistically significant association of any intraoperative surgical variables and the rate of macular hole closure (Table 3).

Multivariate Analysis of Factors Affecting Final Visual Acuity

Multivariate analysis demonstrated a statistically significant association between better preoperative visual acuity ($p<0.001$) and better final visual acuity post-operatively, and an association between macular hole closure ($p<0.001$) and better final visual acuity post-operatively (Table 3). There was also a statistically significant association between preoperative diagnosis and final VA postoperatively ($p=0.026$; primary MH final logMAR VA 0.838±0.142, refractory MH final logMAR VA 1.063±0.123, MH-RRD final logMAR VA 1.403±0.322); patients with macular holes, whether primary or refractory, were more likely to have better final visual acuity than patients with MH-RRD (Table 3). Nevertheless, patients with complex MH-RRD were more likely to gain 3 or more, as well as 5 or more, lines of VA compared to either of the other MH groups (compare Tables 2A-2C). There were no statistically significant associations between any other preoperative patient characteristics or any intraoperative surgical variables and final visual acuity (Table 3).

For anatomic outcomes of macular hole closure based on OCT, there was a significantly better final visual acuity for patients with reconstitution of the ellipsoid zone (EZ) band (p=0.02) and those with alignment of the neurosensory layers (ANL; p=0.01). There was no significant association between final visual acuity and any other anatomic variable (Table 3).

The Effect of Tamponade Agent on Outcomes for All Cases

In 78 cases, silicone oil was used for tamponade (60%), compared to 26 cases with PFO (20%), compared to 26 cases with gas (20%). There was no significant difference between tamponade agent and macular hole closure rate (p=0.939), nor for the presence of transient postoperative hyperreflectivity suggestive of graft hypoxia (p=0.357). Nor was there a significant difference for tamponade agent and final visual acuity (p=0.10) or change in visual acuity from preop to final (p=0.071), though there was a trend towards better visual acuity in cases with PFO tamponade (final logMAR VA 1.03±0.20; change in logMAR VA -0.17±0.03) compared to SO (final logMAR VA 1.13±0.13; change in logMAR VA -0.38±0.04). There was a trend towards better final VA in cases with gas tamponade (final logMAR VA 0.84±0.17; change in logMAR VA -0.27±0.05), compared to both PFO and SO. However, when adjusting for preoperative diagnosis and preoperative VA, there was no significant difference in final VA or change in VA for any tamponade agent. Given the small number of cases, varying preoperative diagnoses, and confounding variables, a larger study would be needed to further assess the effect of intraoperative tamponade agent on outcomes.

Subgroup Analysis for Patients with a Final Visual Acuity of 20/50 or Better

Twelve percent (n=15) of patients achieved a final visual acuity of 20/50 or better. Mean age was 65.3±20.7, 53% (n=8) were female, 50% African, 30% Asian, and 20% Caucasian. Preoperative diagnosis was primary macular hole for 33.3% of patients (n=5) and refractory macular hole (with a mean number of previous surgeries of 1.4±0.4) for 66.7% (n=12) of these patients. There were no cases of combined macular hole – rhegmatogenous retinal detachment in this subgroup. Mean maximum macular hole diameter was 1650±520 and mean minimum macular hole diameter was 816±258. Mean spherical equivalent was -0.83±0.29 and mean axial length was 22.3±7.4. Sixty percent of patients were phakic. Preoperative mean logMAR visual acuity was 0.848±0.219 (Snellen equivalent of 20/140), and it improved significantly to 0.308±0.079 (Snellen equivalent of 20/40; p<0.001). Mean follow-up was 9.3±2.4 months.

Neurosensory retina was harvested in 86% of these cases compared to both retina and choroid in 14% of cases. The graft was taken from posterior to the equator in 80% of cases compared to anterior to the equator in 20% of cases. The location of harvest site was inferonasal in 62%, superonasal in 25%, and superotemporal in 13%. Sixty-seven percent of grafts were sized to position edge-to-edge with the perifoveal host border, while 33% of grafts were sized to overlap with the perifoveal host border. Sixty percent of grafts were placed preretinally or at the level of the retina compared to 40% being subretinally. Gas was used as tamponade in 54% of cases, compared to silicone oil in 31%, compared to PFO in 15%. In cases with silicone oil tamponade, a fluid-to-air-to-silicone-oil exchange was performed in 60% of cases compared to a direct PFO to SO exchange in 40%.

On analysis of OCT images, 80% of cases had reconstitution of the ELM, 67% of cases had complete reconstitution of the EZ Band, and 7% of cases had partial reconstitution of the EZ Band. Alignment of neurosensory layers occurred in 44% of these cases. Microperimetry was available for 3 cases of this subgroup and showed improved fixation at the graft with a mean response of 11.3 ± 6.5 dB. Given the small subset of data, definitive conclusions regarding microperimetry could not be drawn.

Multivariate analysis revealed that patients with VA≥20/50 were more likely to have a preoperative diagnosis of primary or refractory macular hole than combined MH-RRDs (p=0.008). There was no statistically significant association for any other preoperative characteristic. Patients with VA≥20/50 were more likely to have grafts harvested from posterior rather than anterior to the equator (p=0.007). There was no statistically significant association for any other intraoperative surgical variable. Complete reconstitution of the EZ band (p=0.039) and alignment of neurosensory layers (p=0.022; ANL) on OCT were found to be associated with better final visual acuity. All of the cases in this subgroup had closure of the macular hole (100%).

Ancillary Testing following Autologous Retinal Transplantation

OCT angiography (OCTA) was performed for 11 cases. Due to the small number, varying devices used, and non-standardized approach in image collection, quantitative analysis could not be performed. Qualitatively, there appeared to be some limited, secondary vascularization into the region of the graft, in both the superficial and deep capillary plexus (Figure 3). In the superficial capillary plexus, a pattern of tangential secondary growth of vessels to anastomose with other vessels circumferential to the graft was noted in some cases. Vessel growth tended to be limited, and often erratic, with large avascular patches noted on long-term follow-up. The subset of images was too small to draw definitive conclusions about post-transplantation secondary vascularization.

Microperimetry, which was performed in 12 cases, showed a mild, but credible increase in fixation corresponding to the ART graft. The mean response was 6.7 ± 1.9 dB. Given the small subset of data, definitive conclusions regarding microperimetry could not be drawn. A multifocal electroretinogram (mfERG) was performed in 3 cases. The mfERG showed slow, but measurable b-wave amplitudes in the region corresponding to the ART graft. Given the small data set, definitive conclusions could not be drawn.

Discussion

Surgical techniques for the repair of macular holes have undergone a stepwise evolution since the initial reports of vitrectomy and gas tamponade in the early 1990's.[6,20] The initial reports were met with widespread skepticism and debate as to the efficacy; some wondered whether vitrectomy should be the modality of choice for addressing macular holes.[21,22] The field has come a long way since that time.

Vitrectomy, intraocular gas tamponade, and face down positioning has shown good efficacy for closing smaller macular holes, although persistent macular holes and late reopening (recurrence) of closed holes have been reported.[23] The initial technique was useful for addressing one of the most important mechanisms of typical macular hole formation: antero-posterior traction. Tangential traction may have also been treated in some cases with residual adherent cortical vitreous or with an epiretinal membrane noted on biomicroscopy if peeled intraoperatively. After the advent of optical coherence tomography, the technique was subsequently taken a step further by introducing peeling of the ILM, which enhanced the possibility of closing larger holes and addressed tangential traction.[9] The advent of the inverted ILM flap has further enhanced our surgical armamentarium for addressing large and myopic macular holes.[11] Additional surgical modifications to this technique have included, the use of viscoat, blood, or PFO as an adjuvant.[24,25]

The emergence of human amniotic membrane (hAM) grafts in 2019 for the treatment of refractory macular holes, as well as MH-RRD, similarly to autologous retinal transplantation (introduced in 2016), has unlocked the potential for treating previously untreatable pathology, by way of grafting.[5,26-29] Early anatomic and functional results of hAM for patients with refractory macular holes and MH-RRD, are encouraging. Larger series and global collaborations will continue to inform our experience with the technique. It is difficult to draw comparisons between the surgical techniques for macular hole closure from the various publications, given the small size of the studies, diverse variability in the pathology, including macular hole diameter and axial length, significant variation in surgical techniques, and lack of randomization. A large, randomized, controlled clinical trial could offer further insights.

The advent of Autologous Retinal Transplantation (ART), has generated new and interesting clinical questions: How does the graft survive from the metabolic standpoint? How does a piece of peripheral retina respond functionally when translocated to the posterior pole? What happens anatomically at the graft donor-host border; how does the graft integrate?

In primary macular hole cases, 53% showed a transient hyperreflectivity of the ART graft on OCT, compared to 39% in refractory macular hole cases, compared to 53% in combined macular hole – rhegmatogenous retinal detachment (MH-RRD) cases, suggestive of transient hypoxia. This hyperreflectivity was seen predominantly in the first post-operative week, and resolved in all cases, by about post-op month 1, without thinning of the graft. OCTA was performed in 11 cases, and in that small subset of patients, there was the qualitative suggestion of limited, secondary vascularization into the graft. The pattern of blood vessel growth was often tangential, with new vessels anastomosing with old vessels, circumferentially around the graft; but this growth was usually limited and erratic, with large avascular patches (Figure 3). It is likely that the graft depends on diffusion of oxygen from the choroid, adjacent retina, and vitreous cavity for its survival in the early post-operative period. The post-operative angiogenesis noted herein was similar to previously published work showing partial vascular reperfusion of the transplanted retina within 6 weeks that further vascularizes by 3 months post-operatively; there were also small areas of vascular leakage noted, suggestive of fine retinal neovascularization at the graft-host junction.[30] Taken together, vascular patterns at the graft-host junction after ART suggest that there is an angiogenic stimulus promoting late vascularization of the transplant.

Silicone oil blocks the transfer of oxygen between the retina and the anterior chamber after vitrectomy.[31,32] It may then possibly reduce oxygen diffusion to the transplant, which may be better facilitated under PFO.[33] In 78 cases, silicone oil was used for tamponade, compared to 26 cases with PFO, compared to 26 cases with gas. Subanalysis showed that there was no significant difference between tamponade agent and macular hole closure rate (p=0.939), presence of transient postoperative hyperreflectivity (p=0.357), final visual acuity (p=0.10), nor for change in visual acuity from preop to final (p=0.071). Future studies with hyperspectral imaging at various post-operative time points could help us understand oxygenation and perfusion patterns of the transplant in the setting of various tamponade agents, given the better theoretical diffusion of oxygen through perfluorocarbon liquids relative to silicone oil and gas tamponade.

A multivariate analysis revealed that there was no statistically significant difference for any of the surgeon-modified intraoperative variables and final anatomic outcome or final visual acuity (Table 3). Nor were there differences in outcomes between surgeons. This suggests that this technique can be successfully performed by surgeons across the world, with modification of the previously mentioned intraoperative variables, to address previously untreatable macular holes. This, however, does not exclude that a specific peripheral retinal location in a specific patient, in a specific eye, may be the best source for an autologous transplant. In the subgroup with better final VA better or equal to 20/50, 87% of grafts were from a nasal location (combined superonasal and inferonasal). However, after adjusting for other confounding variables, location of the graft was not significantly associated with better outcomes. Further studies, including advanced imaging such as adaptive optics and hyperspectral imaging may help answer some of these questions and guide us to the ideal location in a given eye.

A technique for transplanting combined neurosensory retina and retinal pigment epithelium plus choroid for the treatment of advanced fibrosis from age-related macular degeneration with or without concomitant macular hole showed positive functional and anatomic outcomes.[2] Within the present study, there was no difference in outcomes for neurosensory graft versus combined neurosensory, RPE, and choroid graft, but the sample size was likely too small to truly detect a difference, but at least may show that the combined procedure, which is more complex, is tolerated with reasonable outcomes for advanced pathology.

There were a number of interesting post-operative findings on OCT relative to the anatomy of the ART graft. Across all cases, there was a 55.0% rate of reconstitution of the ELM at 2.28±0.42 months, 52.5% rate of reconstitution of the EZ band at 3.52±0.47 months, and a 16.3% rate of alignment of neurosensory layers (ANL), a novel OCT finding. In cases with ANL, the layers between the donor graft and host retina appear to line up anatomically (e.g. inner plexiform to inner plexiform, outer plexiform to outer plexiform, etc). A vertical striation or dividing line between the graft and host tissue was noted in the first post-operative week in many cases, and it resolved typically by the first or second postoperative month, as the graft integrated with the host retina. Reconstitution of the EZ band (p=0.02) and ANL (p=0.01) on OCT were found to be associated with better final visual acuity and may serve as important prognostic, post-operative biomarkers.

Autologous retinal transplantation led to anatomical and functional improvement in the treatment of primary and refractory macular holes, as well as combined MH-RRDs. These results suggest that a vitreoretinal surgeon may consider grafting techniques for large, primary macular holes, or if a macular hole failed to close by traction-relieving techniques, such as vitrectomy, ILM peeling, or ILM flaps with gas tamponade. In this study, 25% of patients with refractory macular holes (all of whom had their ILM peeled previously), gained 5 or more lines of vision. Thus, patients have a meaningful opportunity for a better functional outcome if ART or grafting surgery is performed, as evidenced by the visual gains in the refractory macular hole group.

One limitation of this study is that we did not have sufficient data available on the chronicity of the macular holes in this series. Such data could be helpful in determining if there are differential outcomes based on the timing of macular hole repair. This may also explain, in part, the similar outcomes between primary and refractory holes. If cases in the primary macular hole group were chronic, functional outcomes may have had a reduced opportunity for visual gains. Furthermore, the majority of patients in this group were phakic, compared to the majority in the refractory macular hole group being pseudophakic; there was no difference in the rate of cataract surgery between the two groups during the study period.

In the MH-RRD group, there was a 95% macular hole closure rate. Part of the VA gains in the MH-RRD group are due to the reattachment of the retina and not necessarily macular hole closure. Importantly, the presence of macular hole in many of these cases is also the cause of the retinal detachment, and thus achieving closure is important for reattachment of the retina. There was a 79% rate of retinal attachment in the MH-RRD group with a single surgery. By the date the study was closed, in 66.7% of these cases, the final tamponade agent (SO, PFO, gas) had been removed or resolved.

Additionally, 12% of patients in this study reached 20/50 visual acuity or better. This merits further exploration as to the role and potential of peripheral retina in acquiring macular resolution, which could then be a sign of hope for other macular diseases. Indeed, neural stem and progenitor cells have been detected in the vicinity of the peripheral retina in humans. Those may become activated in response to injury and detachment with proliferative vitreoretinopathy.[3,34-36] Some of those cells could have been included in autologous retinal graft tissue and helped achieve better visual outcomes. Additionally, in animal models where cones were absent, rod photoreceptors formed functional ectopic synapses to cone bipolar cells.[37] Whether rod photoreceptors from peripheral grafts could behave similarly remains to be determined. Rod photoreceptor transplantation in a pig model, restored glucose transport in the subretinal space, and helped regenerate cone synthesis and electrophysiologic function.[38] Furthermore, rod photoreceptor transplantation can reactivate and support dormant cone inner and outer segments at the edges of the macular hole, reversing end-stage dormancy, and restoring visual function.[38] Restoration of structure of those cones and potential migration into the graft may be reflected in the reconstitution of the EZ and ANL, and it may explain some of the functional gains. Indeed, EZ band reconstitution after macular hole surgery has been previously found to be significantly associated with better post-operative vision.[39,40]

We also feel that anatomical closure can be achieved in close to 100% of large, chronic, and unusual macular holes. This technique was relatively new at the time of surgery for a number of surgeons worldwide, and outcomes may improve with experience. Since subretinal placement of the graft did not differ from preretinal positioning, and since PFO can help secure the graft in place, additional manipulation of the graft to tuck its edge under the macular hole edge may be unnecessary. Positioning the graft in the same plane as the surrounding tissue may give it the best opportunity to form edge to edge connections and stimulate alignment of the neurosensory layers (ANL). Though not easily achieved, cases with ANL had better functional outcomes. Even if slight movement of the graft occurs, and is detected by OCT postoperatively, the graft can be readjusted at the time of PFO removal at 2 weeks. ANL may also partially explain the resolution of the central scotoma in patients undergoing ART, and connection with surrounding ganglion cells may increase the receptive field, changing a positive into a negative scotoma.

Interestingly, there was a high rate (75%) of discrete, round, hyperreflective foci noted in the graft in the early post-op period; similar findings have been previously reported to be microglia in non-human primates, playing a role in the wound healing and immunological response of the retina.[41] A larger study as well as *ex vivo* or post-mortem immunohistopathology studies could shed further light on this finding. The presence of these hyperreflective foci did not appear to have an effect on anatomic or functional outcomes in this study.

Another important consideration from the present study is on the nomenclature of macular holes. The classic nomenclature defines a large macular hole as having a diameter of 400 micrometers. The average macular hole in this study was 1170±70 micrometers. The advent of grafting procedures to complement traction-relieving techniques for closing macular holes, has allowed surgeons the opportunity to close macular holes that were previously thought to be too large to be adequately addressed surgically, and with functional improvement. In some ways, grafting surgery has created a need for an update to the classification system for macular holes to address this appreciably larger subset. At what macular hole diameter would a grafting technique be a better first choice over a traction-relieving technique?

While data regarding microperimetry (n=12) and multifocal electroretinography (n=3) was limited, the results were interesting. The mean response of the ART graft on microperimetry was 6.7±1.9 dB. Cases with mfERG showed slow, but measurable b-wave amplitudes in the ART graft. Further study with a larger array of data is needed.

Limitations of this study include its retrospective design with ancillary tests available in some cases and not others, the lack of comprehensive data regarding the chronicity of macular hole duration or changes in vision for all cases, the lack of a control or comparative group, and the variability of surgical techniques between surgeons. To better understand the efficacy, safety, and cost of ART relative to other surgical techniques of macular hole closure (e.g. vitrectomy with ILM peel or flap, amniotic membrane graft, etc), an international, multicenter, randomized, single-masked, prospective clinical trial could be designed, including standardized ancillary testing with OCT, OCTA, autofluorescence, microperimetry, multifocal ERG, and adaptive optics at prespecified timepoints. Post-mortem histopathology and *ex vivo* studies in monkey eyes or porcine eyes could help us better understand the OCT finding of Alignment of Neurosensory Layers and its significance.

In conclusion, 130 ART surgeries were performed by 33 vitreoretinal surgeons globally, for patients with complex pathology. Patients achieved anatomical and functional improvement with low complication rates. Patients came from diverse backgrounds representative of a truly global project. This group of patients had macular holes that were several times larger than the lower limit of "large" based on the traditional classification of 400 micrometers. Importantly, 43% of patients experienced a 3-line gain in visual acuity, 29% of patients gained at least 5-lines of vision, with an 89% macular hole closure rate (78.5% complete, 10% small eccentric defect), with a 95% closure rate in MH-RRD (68.4% complete, 26.3% small eccentric defect). Twelve percent of patients achieved 20/50 vision or better, suggesting excellent graft function. We are hopeful that this global study will stimulate further research on autologous retinal transplantation and provide guidance in the surgical management of complex macular holes.

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Figure and Table Legends

Table 1. Demographics and Preoperative Characteristics for Patients Undergoing Autologous Retinal Transplantation for Repair of Primary MHs, Refractory MHs, and Combined MH-RRDs.

Table 2A. Anatomic and Functional Outcomes for Patients with Primary Macular Holes Undergoing Autologous Retinal Transplantation.

Table 2B. Anatomic and Functional Outcomes for Patients with Refractory Macular Holes Undergoing Autologous Retinal Transplantation.

Table 2C. Anatomic and Functional Outcomes for Patients with Combined MH-RRDs Undergoing Autologous Retinal Transplantation.

Table 3. The Effect of Preoperative Characteristics and Intraoperative Surgical Variables on Anatomic and Functional Outcomes.

Figure 1. OCT findings after autologous retinal transplantation (ART). (A) OCT pre-operatively shows a macular hole with minimum diameter of 692 μm and maximum diameter of 1420 μm. (B) OCT post-op week 2 after ART shows early integration of the graft and partial reconstruction of the external limiting membrane (ELM) and ellipsoid zone (EZ) band (yellow arrows). There are multiple hyperreflective foci within the graft suggestive of microglia (red arrows). (C) At post-op month 1, there is further reconstitution of the ELM and EZ band and a decrease in the hyperreflective foci. (D) By post-op month 3, there is complete reconstitution of the ELM and EZ band.

Figure 2. Integration of the transplanted autologous donor graft into the host tissue. (A) At post-op week 1, there is early integration of the transplant, with vertical striation lines noted between the donor graft and host tissue (dotted yellow arrows). The plexiform layers appear to align with plexiform layers, nuclear layers with nuclear layers, and so forth (solid yellow arrows). There is also hyperreflectivity noted within the graft. (B) By post-op month 3, there is resolution of the vertical striation lines, and there appears to be continued alignment of the neurosensory layers between donor and host tissue. In cases where apparent alignment between donor and host was observed, a novel OCT finding of "alignment of neurosensory layers" (ANL) is reported.

Figure 3. Optical coherence tomography angiography changes after autologous retinal transplantation. (A) Structural B-scan showing integration of the autologous retinal transplant graft at post-op week 1. (B) En face optical coherence tomography angiography (OCTA) image of the superficial vascular plexus (SVP), showing hyporeflectivity and absence of vessels centrally within the area of the graft, while the preoperative host vessels elsewhere in the macula are intact. (C) These post-op week 1 findings are also noted within the deep vascular plexus (DVP), with absence of vascularity immediately surrounding the graft. (D) OCTA at post-op month 2 shows increased density of small arterioles, venules, and capillary networks in the vicinity immediately around the graft within the SVP. (E) There is also increased density of vessels noted within the DVP at post-op month 2. This suggests that there is secondary vascularization and vascular remodeling that occurs around the transplant over time.

Video 1. Representative surgical video demonstrating autologous retinal transplantation in an eye with a refractory macular hole. Foot-pedal activated, pneumatic, vertical scissors were used to excise the graft in a site superiorly, posterior to the equator. Graft excision and transfer to the final transplantation position were carried out underneath perfluorocarbon heavy liquid (PFO) to ensure graft stability and to maintain correct orientation of the graft. In this case, a direct PFO to silicone oil (SO) exchange was performed, with SO as the final tamponade.

Video 2. Representative surgical video demonstrating autologous retinal transplantation (ART) in an eye with a combined macular hole – rhegmatogenous retinal detachment and pathologic myopia. The eye has previously undergone vitrectomy, laser, and silicone oil tamponade. Due to contraction of the inferior retina and recurrent detachment under silicone oil, retinectomy is necessary. A peripheral ART harvest site is selected. The retinectomy is initiated and completed at the harvest site. Chandelier endoillumination is used to allow for bimanual techniques. After freeing the posterior border of the graft with the vitrector, the graft is stabilized and held with end-grasping forceps, while the anterior border is excised with the vitrector. The graft is then positioned overlying the macular hole, and held in place with the forcep, while perfluorocarbon liquid (PFO) is slowly delivered as a single bubble. A PFO fill is achieved and the retina is attached. After treating the retinectomy and harvest site borders with several rows of endolaser, PFO is left as the final tamponade, due to its desirable oxygen diffusion and tamponade properties, with a plan to remove it in a few weeks and exchange it for long-acting gas. In the early post-operative weeks, the graft depends on diffusion of oxygen for its survival.

Table 1. Demographics and Preoperative Characteristics for Patients Undergoing Autologous Retinal Transplantation for Repair of Primary MHs, Refractory MHs, and Complex Combined RRD-MHs

# of Patients	130		
Mean Age (years)	62.9	±	6.3
Females	58.5%		
Males	41.5%		
Caucasian	41.6%		
African	22.8%		
Asian	18.8%		
Latino	16.8%		
Mean maximum MH diameter (µm)	1470	±	165
Mean minimum MH diameter (µm)	837	±	94
Mean spherical equivalent	-3.4	±	0.4
Mean axial length (mm)	24.6	±	3.2
Pseudophakic	49.2%		

Abbreviations: MH, macular hole. RRD, rhegmatogenous retinal detachment.

Table 2A. Anatomic and Functional Outcomes for Patients with Primary Macular Holes Undergoing Autologous Retinal Transplantation

# of Patients	35		26.9%
Mean Age (years)	57.8	±	11.3
Females	51.4%		
Males	48.6%		
Caucasian	11.6%		
African	19.2%		
Asian	42.3%		
Latino	26.9%		
Mean maximum MH diameter (μm)	1480	±	297
Mean minimum MH diameter (μm)	882	±	176
Mean spherical equivalent	-0.9	±	0.2
Mean axial length (mm)	23.1	±	4.9
Pseudophakic	22.9%		
Mean Final Follow-up (months)	8.486	±	1.434
Pre-op Mean LogMAR VA	1.090	±	0.184
Approximate Pre-op VA	20/470		
Final post-op Mean LogMAR VA	0.838	±	0.142
Approximate Post-op VA	20/149		*p = 0.0028* *
% who gained ≥ 3 lines VA	37.1%		
% who gained ≥ 5 lines VA	17.1%		
Macular Holes Closed	30		85.7%
Complete	29		96.7%
Eccentric	1		3.3%
Post-operative, Masked OCT Analysis			
# with acceptable quality and follow-up:	24		

Reconstitution of ELM	13	54.2%
Reconstitution of EZ Band	12	50.0%
Alignment of Neurosensory Layers (ANL)	4	16.7%
Hyper-reflective foci (e.g. microglia)	18	75.0%
Transient Graft Hyper-Reflectivity	8	33.3%
Graft Dislocation	1	2.9%
Retinal Detachment	0	0.0%
Subretinal PFO	0	0.0%
Endophthalmitis	0	0.0%
High IOP requiring treatment	2	5.7%

Abbreviations: #, number. MH, macular hole. Pre-op, pre-operative. LogMAR, Logarithm of the Minimum Angle of Resolution. VA, visual acuity. Post-op, post-operative. ELM, external limiting membrane. EZ, Ellipsoid Zone. PFO, perfluorocarbon liquid. IOP, intraocular pressure.

Table 2B. Anatomic and Functional Outcomes for Patients with Refractory Macular Holes Undergoing Autologous Retinal Transplantation

# of Patients	76		58.5%
Mean Age (years)	66.9	±	8.9
Females	65.3%		
Males	34.7%		
Caucasian	48.2%		
African	21.4%		
Asian	14.3%		
Latino	16.1%		
Mean maximum MH diameter (μm)	1440	±	210
Mean minimum MH diameter (μm)	796	±	117
Mean spherical equivalent	-2.4	±	0.4
Mean axial length (mm)	24.8	±	4.6
Pseudophakic	56.6%		
Mean # of previous PPV / ILM Peel	1.7	±	0.2
Mean Final Follow-up (months)	8.6	±	1.0
Pre-op Mean LogMAR VA	1.258	±	0.144
Approximate Pre-op VA	20/362		
Final post-op Mean LogMAR VA	1.063	±	0.123
Approximate Post-op VA	20/231		*p = 0.0019 **
% who gained ≥ 3 lines VA	36.8%		
% who gained ≥ 5 lines VA	25.0%		
Macular Holes Closed	67		88.2%
Complete	60		89.6%
Eccentric	7		10.4%

Post-operative, Masked OCT Analysis		
# with acceptable quality and follow-up:	39	
Reconstitution of ELM	26	66.7%
Reconstitution of EZ Band	26	66.7%
Alignment of Neurosensory Layers (ANL)	8	20.5%
Hyper-reflective foci (e.g. microglia)	19	48.7%
Transient Graft Hyper-Reflectivity	15	38.5%
Graft Dislocation	3	3.9%
Retinal Detachment	1	1.3%
Subretinal PFO	0	0.0%
Endophthalmitis	1[†]	1.3%
High IOP requiring treatment	2	2.6%

Abbreviations: #, number. MH, macular hole. PPV, pars plana vitrectomy. ILM, internal limiting membrane. Pre-op, pre-operative. LogMAR, Logarithm of the Minimum Angle of Resolution. VA, visual acuity Post-op, post-operative. ELM, external limiting membrane. EZ, Ellipsoid Zone. PFO, perfluorocarbon liquid. IOP, intraocular pressure.

[†] One case of possible endophthalmitis was treated with intravitreal tap and injection of antibiotics; the culture was negative.

Table 2C. Anatomic and Functional Outcomes for Patients with Combined, Complex RRD-MH Undergoing Autologous Retinal Transplantation

# of Patients	19		14.6%
Mean Age (years)	58.2	±	13.4
Females	47.4%		
Males	52.6%		
Caucasian	63.2%		
African	31.6%		
Asian	0.0%		
Latino	5.3%		
Mean maximum MH diameter (µm)	1630	±	576
Mean minimum MH diameter (µm)	933	±	330
Mean spherical equivalent	-10.3	±	2.9
Mean axial length (mm)	28.0	±	9.3
Pseudophakic	68.4%		
Mean # of previous PPV	1.5	±	1.4
Mean Final Follow-up (months)	8.9	±	2.0
Pre-op Mean LogMAR VA	2.316	±	0.531
Approximate Pre-op VA	HM		
Final post-op Mean LogMAR VA	1.403	±	0.322
Approximate Post-op VA	20/506		*$p < 0.001$ **
% who gained ≥ 3 lines VA	73.7%		
% who gained ≥ 5 lines VA	68.4%		
Macular Holes Closed	18		94.7%
Complete	13		72.2%
Eccentric	5		27.8%

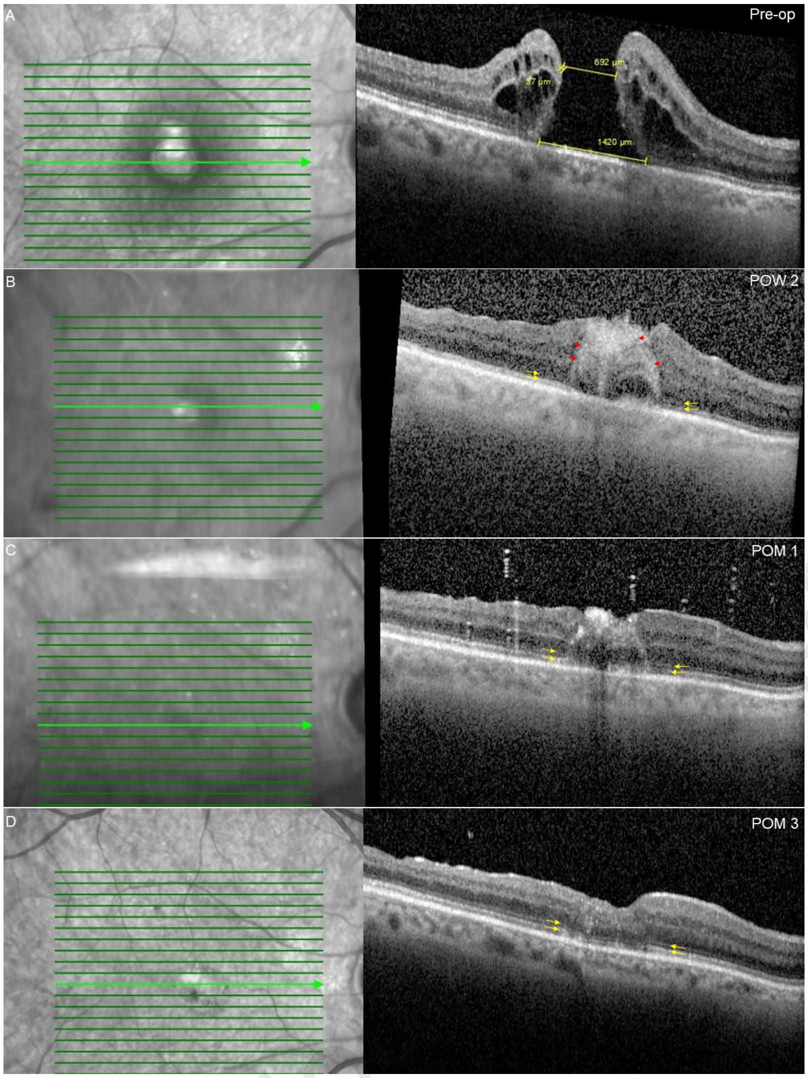
Post-operative, Masked OCT Analysis		
# with acceptable quality and follow-up:	17	
Reconstitution of ELM	5	29.4%
Reconstitution of EZ Band	4	23.5%
Alignment of Neurosensory Layers (ANL)	1	5.9%
Hyper-reflective foci (e.g. microglia)	10	58.8%
Transient Graft Hyper-Reflectivity	9	52.9%
Graft Dislocation	1	5.3%
Retinal Detachment	4	21.1%
Subretinal PFO	2	10.5%
Endophthalmitis	0	0.0%
High IOP requiring treatment	1	5.3%

Abbreviations: RRD-MHs, rhegmatogenous retinal detachment and macular hole. #, number. MH, macular hole. PPV, pars plana vitrectomy. Pre-op, pre-operative. LogMAR, Logarithm of the Minimum Angle of Resolution. VA, visual acuity. HM, Hand motion. Post-op, post-operative. ELM, external limiting membrane. EZ, Ellipsoid Zone. PFO, perfluorocarbon liquid. IOP, intraocular pressure.

Table 3. The Effect of Preoperative Characteristics and Intraoperative Surgical Variables on Anatomic and Functional Outcomes

		MH Closure (*p-value*)	Final VA (*p-value*)
Preoperative Characteristics	Age	0.87	0.55
	Gender	0.90	0.36
	Race	0.54	0.46
	Diagnosis	0.33	**0.026 ***
	Max. MH diam.	0.95	0.24
	Min. MH diam.	0.80	0.52
	Previous ILM Peel	0.93	0.66
	Previous # of PPV	0.53	0.45
	Mean Sph.Eq.	0.38	0.24
	Mean Axial Length	0.61	0.19
	Lens Status	0.72	0.67
	Preop VA	0.27	**<0.001 ***
Intraoperative Variables	PPV Gauge	0.70	0.64
	Type of Graft	0.68	0.97
	Harvest Octant	0.98	0.63
	Harvest Site	0.81	0.49
	Size of Graft	0.77	0.12
	Graft Placement	0.52	0.13
	Graft Fit	0.54	0.96
	Tamponade Agent	0.94	0.10
	Tamponade Exchange	0.53	0.18
Postoperative OCT Findings	Macular Hole Closure	-	**<0.001 ***
	Reconstitution of ELM	-	0.15
	Reconstitution of EZ Band	-	**0.02 ***
	Alignment of Neurosensory Layers	-	**0.01 ***
	Hyper-reflective foci (microglia)	-	0.3
	Transient Graft Hyper-Reflectivity	-	0.63

Abbreviations: MH, macular hole. Diagnosis compares primary MHs, refractory MHs, and complex combined RRD-MHs. Max, maximum. Diam, diameter. ILM, internal limiting membrane. PPV, pars plana vitrectomy. Sph, spherical. Eq, equivalent. Preop, preoperative. VA, visual acuity. Type of graft compares neurosensory retina to neurosensory retina with retinal pigment epithelium and choroid. Harvest octant compares graft locations of superonasal, superior, superotemporal, temporal, inferotemporal, inferior, inferonasal, nasal. Harvest site compares posterior to anterior to the equator. Graft placement compares preretinal to subretinal positioning. Graft fit compares edge to edge to preretinal. Tamponade agent compares silicon oil (SO) to perfluorocarbon liquid (PFO) to gas. Tamponade exchange compares direct PFO to SO exchange, PFO to air to SO, PFO to air to gas. ELM, external limiting membrane. EZ, Ellipsoid Zone.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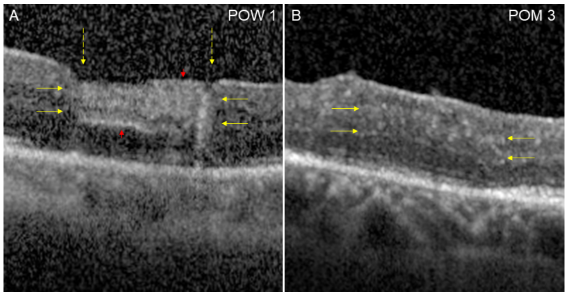
1420 µm
B
POW 2
C
POM 1
D
POM 3


A
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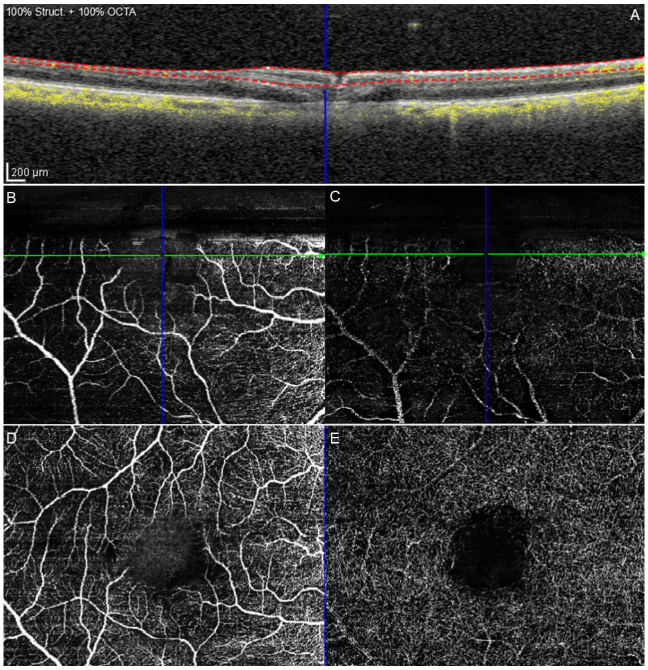
POM 3


100% Struct. + 100% OCTA
A
200 µm
B
C
D
E

Précis

In a global consortium of surgeons, autologous retinal transplantation resulted in anatomic closure of 89% for large, giant, and myopic, primary macular holes, refractory macular holes, and macular holes associated with a retinal detachment. Visual acuity improved by at least 3-lines in 43% of eyes. ART graft dislocation occurred in 3.8% of eyes.